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ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GR--ETC F/G 6/20
TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENT--ETC(U)
MAR 81 M J TOPPER, M H WEEKS
UNCLASSIFIED USAEHA-75-51-0156-81

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UNITED STATES ARMY
ENVIRONMENTAL HYGIENE
AGENCY

ABERDEEN PROVING GROUND, MD 21010

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USAEHA-75-51-0157-91.

TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENTS
AI3-37543 and AI3-37546
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS
~~STUDY NOS. 75-51-0156-81 AND 75-51-0158-81~~
SEPTEMBER 1978 - DECEMBER 1980.

Michael S. Topp
Marion H. White

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COLLECTED
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Final Rpt 78- Dec 80

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Preliminary hazard evaluation of AI3-37543 and AI3-37546 were performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. The technical grade chemicals did not cause skin, eye, or photo irritation. They did not prove to be acutely toxic by ingestion. It was recommended that both chemicals be approved for further testing as candidate insect repellents.		

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U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

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REPLY TO
ATTENTION OF

HSE-LT-T/WP

9 MAR 1981

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellents
AI3-37543 and AI3-37546, US Department of Agriculture Proprietary
Chemicals, Study Nos. 75-51-0156-81 and 75-51-0158-81, September
1978 - December 1980

Executive Secretary
Armed Forces Pest Management Board
Forest Glen Section, WRAMC
Washington, DC 20012

A summary of the pertinent findings and recommendations of the inclosed
report follows:

Preliminary hazard evaluations of AI3-37543 and AI3-37546 were performed by
means of laboratory animal studies using rats, rabbits, and guinea pigs. The
technical grade chemicals did not cause skin, eye, or photo irritation. They
did not prove to be skin sensitizers or to be acutely toxic by ingestion. It
was recommended that both chemicals be approved for further testing as
candidate insect repellents.

FOR THE COMMANDER:

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

REPLY TO
ATTENTION OF

HSE-LT-T/WP

TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENTS
AI3-37543 and AI3-37546
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS
STUDY NOS. 75-51-0156-81 AND 75-51-0158-81
SEPTEMBER 1978 - DECEMBER 1980

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man Research Laboratory, Gainesville, Florida, 27 September 1978.

b. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of the Army, Office of The Surgeon General; the Armed Forces Pest Control Board; and the US Department of Agriculture, Agricultural Research, Science and Education Administration, titled, Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. REFERENCE. Toxicology Division Procedural Guide, US Army Environmental Hygiene Agency (USAEHA), 1972, revised 1976.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellents AI3-37543 and AI3-37546.

4. SUMMARY OF FINDINGS. Hazard evaluation of the candidate repellents AI3-37543 and AI3-37546 were conducted by this Agency using New Zealand White rabbits for skin and eye studies, Hartley guinea pigs for a skin sensitization study, and Sprague-Dawley rats for determination of oral toxicity. A tabular presentation of animal toxicity data developed in this Agency follows:*†

* In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," US Department of Health, Education and Welfare Publication No. (NIH) 74-23, revised 1978.

† The experiments reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

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Study Nos. 75-51-0156-81 and 75-51-0158-81, Sep 78 - Dec 80

TABLE. PRESENTATION OF DATA

Test	Results	Interpretation
<u>SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application to intact and abraded skin of New Zealand White rabbits.	Chemicals AI3-37543 and AI3-37546 did not cause irritation of the intact skin or of the skin surrounding an abrasion.	USAEHA Category I (ref Appendix A)
0.5 mL technical grade chemical applied to each of six rabbits.	(See Appendices B and C for details.)	
<u>EYE IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application of 0.1 mL technical grade chemical to one eye of each of six New Zealand White rabbits.	Chemicals AI3-37543 and AI3-37546 did not cause irritation to the eyes of rabbits. (See Appendices D and E for details.)	USAEHA Category A (ref Appendix A)
<u>APPROXIMATE LETHAL DOSE (ALD)</u>		
<u>Oral</u>		
Rats (male)-no diluent	AI3-37543 ALD < 1270 mg/kg AI3-37546 ALD = 1270 mg/kg	Neither chemical presents a lethal hazard from accidental ingestion.

Study Nos. 75-51-0156-81 and 75-51-0158-81, Sep 78 - Dec 80

Test	Results	Interpretation
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PHOTOCHEMICAL SKIN IRRITATION STUDIES

Rabbits

A single 0.05 mL application of a 25-percent (w/v) solution of each chemical and a 10 percent (w/v) Oil of Bergamot solution (positive control) in 95 percent ethyl alcohol were applied to the intact skin of six rabbits. Five minutes after application, the rabbits were exposed to UV light (365 nm) for 30 minutes at a distance of 10-15 cm.	A 25-percent solution of AI3-37543 and AI3-37546 in ethanol did not cause photochemical irritation reaction under test conditions. (See Appendices F and G.)	Chemicals AI3-37543 and AI3-37546 did not cause a photochemical irritation reaction under test conditions and are not expected to cause a photochemical irritation in humans.
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Control

Following UV exposures of the rabbits, 0.05 mL of test chemical, positive control and diluent were applied to additional skin areas to serve as unirradiated control sites. Application areas were checked for skin irritation at 24, 48 and 72 hours.	Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas.
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Study Nos. 75-51-0156-81 and 75-51-0158-81, Sep 78 - Dec 80

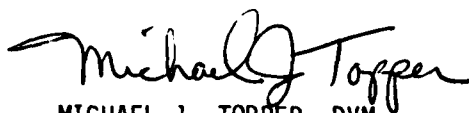
Test	Results	Interpretation
<u>SENSITIZATION STUDIES</u>		
<u>Guinea Pigs (Male)</u>		
Intradermal injections of 0.1 mL of a 0.1 percent solution (w/v) of AI3-37543 and AI3-37546 or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.		
Ten test guinea pigs for each chemical were given 10 sensitizing doses over a 3-week period. After 2 weeks' rest, they were challenged with ID injections of each test chemical.	Challenge doses of AI3-37543 and AI3-37546 did not produce a sensitization reaction. (See Appendices H and I.)	Chemicals AI3-37543 and AI3-37546 did not produce sensitization reactions under test conditions and are not expected to produce sensitization reactions in man.
Ten positive control guinea pigs were sensitized over 3 weeks with DNCB. After 2 weeks' rest, they were challenged with ID injections of DNCB.	Challenge dose of DNCB in positive control guinea pigs produced a marked sensitization reaction in 10 out of 10 guinea pigs.	DNCB produced a marked reaction, indicating the guinea pigs respond to sensitizing agents.

* A known skin sensitizer

Study Nos. 75-51-0156-81 and 75-51-0158-81, Sep 78 - Dec 80

5. CONCLUSION. Technical grade chemicals AI3-37543 and AI3-37546 did not cause any skin, eye, or photo irritation, no sensitization reaction, and did not prove to be an acute ingestion hazard.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that AI3-37543 and AI3-37546 be approved for further testing as candidate insect repellents.



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APPENDIX A

TOPICAL HAZARD EVALUATION PROGRAM
DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING
CONSIDERED FOR ACUTE SKIN APPLICATION

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.)

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation, and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound. (INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.

D. Compounds producing moderate injury to the cornea. INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.

[illegible]

APPENDIX D

COMPOUND: AI3-37543, USDA Proprietary Chemical										USAEHA STUDY NO. 75-51-0156-81																			
ACUTE EYE EFFECTS NEW ZEALAND WHITE RABBITS					USAEHA TOXICITY CATEGORY					CONDITIONS - 0.1 mL applied to right eye of six rabbits. Left eye served as the control.																			
					A																								
																				Time of Reading Hrs-Days	Structure	Scores						Mean Score	Comments
																						Rabbit No.							
					761 762 763 764 765 766																								
24	cornea iris conjunctivae				0 0 0	15 0 6	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	2.5 0 1																	
48	cornea iris conjunctivae				0 0 0	10 0 4	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	1.7 0 0.7																	
72	cornea iris conjunctivae				0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0																	
7-days	cornea iris conjunctivae				0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0																	

APPENDIX E

COMPOUND: A13-37546, USDA Proprietary Chemical				USAEHA STUDY NO. 75-51-0158-81					
ACUTE EYE EFFECTS NEW ZEALAND WHITE RABBITS		USAEHA TOXICITY CATEGORY A				CONDITIONS - 0.1 mL applied to right eye of six rabbits. Left eye served as the control.			
Time of Reading Hrs-Days	Structure	Scores						Mean Score	Comments
		Rabbit No.							
		803	804	805	806	807	808		
24	Cornea	0	0	0	5	0	0	.83	
	Iris	0	0	0	0	0	0	0	
	Conjunctivae	0	0	2	2	0	0	.66	
48	Cornea	0	0	0	0	0	0	0	
	Iris	0	0	0	0	0	0	0	
	Conjunctivae	0	0	0	0	0	0	0	
72	Cornea	0	0	0	0	0	0	0	
	Iris	0	0	0	0	0	0	0	
	Conjunctivae	0	0	0	0	0	0	0	
7-Days	Cornea	0	0	0	0	0	0	0	
	Iris	0	0	0	0	0	0	0	
	Conjunctivae	0	0	0	0	0	0	0	

APPENDIX F

PHOTOCHEMICAL IRRITATION-NEW ZEALAND WHITE RABBITS

COMPOUND: AI3-37543, USDA Proprietary Chemical				USAEHA STUDY NO. 75-51-0156-81				
COMMENTS:								
PROCEDURE: 0.05 mL of a 25% (w/v) solution in 95% ethanol was applied to the backs of six rabbits and 0.05 mL of a 10% solution of Oil of Bergamot was used as the control.								
	MEAN SKIN IRRITATION SCORE							
Observation Time	Test Compound UV Exposure		Test Compound Non-UV Exposure		Positive Control UV Exposure		Positive Control Non-UV Exposure	
	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema
24 Hours	4	1	0	0	12	6	9	4
48 Hours	3	1	0	0	9	5	0	0
72 Hours	0	0	0	0	8	4	0	0
TOTAL	7	2	0	0	29	15	9	4
Mean Irritant Responses	0.39	0.11	0	0	1.51	0.83	0.50	0.22
Net Score								

APPENDIX G

PHOTOCHEMICAL IRRITATION-NEW ZEALAND WHITE RABBITS

COMPOUND: AI3-37546, USDA Proprietary Chemical				USAEHA STUDY NO. 75-51-0159-81				
COMMENTS:								
PROCEDURE: 0.05 mL of a 25% (w/v) solution in 95% ethanol was applied to the backs of six rabbits and 0.05 mL of Oil of Bergamot was used as the control.								
Observation Time	MEAN SKIN IRRITATION SCORE							
	Test Compound UV Exposure		Test Compound Non-UV Exposure		Positive Control UV Exposure		Positive Control Non-UV Exposure	
	Erythema	Edema	Erythema	Edema	Erythema	Edema	Erythema	Edema
24 Hours	10	2	7	0	18	16	10	1
48 Hours	5	1	3	1	15	14	8	3
72 Hours	3	1	1	0	12	11	4	2
TOTAL	18	4	11	1	45	41	22	6
Mean Irritant Responses	1.0	0.22	0.6	0.06	2.5	2.28	1.22	0.33
Net Score								

ACIA Form 62, 1 Feb 81 (REV-11)

APPENDIX H

COMPOUND: AI3-37543, USDA Proprietary Chemical										STUDY No. 75-51-0156-81									
GUINEA PIG SENSITIZATION										Substance: AI3-37543									
MALE																			
HARTLEY STRAIN										Identify:									
										Positive Control: Dinitzochlorobenzene									
Scoring Time 24 hours		Mean Body Wt (G)		Mean Irritation Scores				Comments											
		Initial	Final	Diluent		Test Compound													
Test Compound		Initial	Final	Initial	Final	Initial	Final	Initial	Final										
		466	682	0	0	0	0	0	2.7										
Positive Control		Initial	Final	Initial	Final	Initial	Final	Initial	Final										
		491	736	0	0	0	19	356											
Test Compd 48 hours		Mean Body Wt (G)		Mean Irritation Scores															
		Initial	Final	Diluent		Test Compound													
Test Compound		Initial	Final	Initial	Final	Initial	Final	Initial	Final										
		-	-	0	0	0	0	0	0.9										
Positive Control		Initial	Final	Initial	Final	Initial	Final	Initial	Final										
		-	-	0	0	0	5.4	284											
										Final Scores >100 - Strong Sensitizing 25-100 - Mild Sensitizing <25 - No Sensitizing									

APPENDIX I

COMPOUND: AI3-37546, USDA Proprietary Chemical										STUDY NO. 75-51-0158-81									
GUINEA PIG SENSITIZATION MALE HARTLEY STRAIN										Substance: AI3-37546 Identify: Positive Control: Dinitiochlorobenzene									
Scoring Time 24 hours		Mean Body Wt. (G)		Mean Irritation Scores						Comments									
		Initial	Final	Diluent		Test Compound													
Test Compound		588	801	1.8	0			32		24									
Positive Control		491	736	0	0			19		356									
Test Compd 48 hours		Mean Body Wt. (G)		Mean Irritation Scores															
		Initial	Final	Diluent		Test Compound													
Test Compound		-	-	0.8	0			17.7		19.1									
Positive Control		-	-	0	0			5.4		284									
											Final Scores >100 - Strong Sensitizing 25-100 - Mild Sensitizing <25 - No Sensitizing								

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